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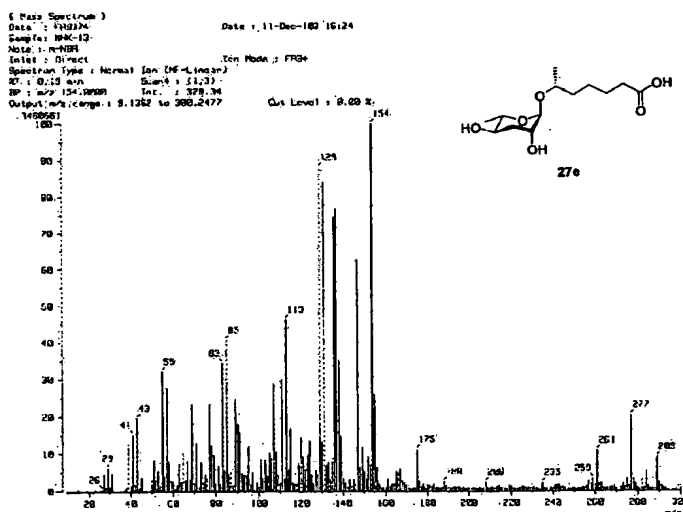
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(54) Title: 6R-(3,6-DIDEOXY-L-ARABINO-HEXOPYRANOSYLOXY)HEPTANOIC ACID, PREPARATION PROCESS FOR  
THE SAME AND DAUER EFFECT THEREOF



(57) Abstract: The present invention relates to a determination of a stereochemistry, a synthesis and dauer effect of 6R-(3,6-dideoxy-L-arabino-hexopyranosyloxy) heptanoic acid as a pheromone isolated from the Caenorhabditis elegans related to suppress of aging and stress. It becomes possible to develop medical substances using the pheromone relating to aging, stress, metabolism, signal transfer system in vivo, and anti-cancer, obesity and a suppressing agent for aging and stress.

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## Description

# 6R-(3,6-DIDEOXY-L-ARABINO-HEXOPYRANOSYLOXY)HEPTANOIC ACID, PREPARATION PROCESS FOR THE SAME AND DAUER EFFECT THEREOF

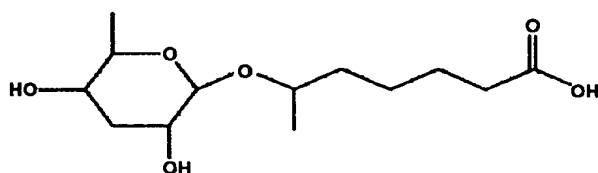
### Technical Field

- [1] The present invention relates to an absolute stereo configuration of 6R-(3,6-dideoxy-L-arabino-hexopyranosyloxy)heptanoic acid related to suppress of aging and stress, a preparation process for the same and dauer effect thereof. More particularly, the present invention relates to a determination of a three-dimensional stereochemistry of 6R-(3,6-dideoxy-L-arabino-hexopyranosyloxy)heptanoic acid that is a pheromone first isolated from *Caenorhabditis elegans*, an intermediate required for synthesis of the same, a preparation method and dauer effect of the pheromone.

### Background Art

- [2] Pheromones, become known as physiological active substance, are defined as substances that are created in a body of animals and secreted out of the body to act on other individuals of the same species, thereby inducing a specific activation or a variation of physiological phenomena.
- [3] According to the previous studies, pheromone secreted from *C. elegans* exists in extremely low concentration, having less than 1,000 Dalton. The pheromone is known as single substance or related compound, which is very stable and non-volatile, having a chromatography property such as short fatty acid hydroxide (Riddle, D.L., Science, 218: 578-580, 1982).
- [4] In the thesis of Riddle, although a pheromone moiety is partially purified, an exact chemical configuration and physical properties of pure pheromone are not known yet. In addition, since a pheromone extract from of *C. elegans* used by the researchers is a crude extract partially purified, there is no way to study for finding an exact physiological target and biological mechanisms.
- [5] Therefore, the inventors of the present invention mass-cultured *C. elegans* containing the pheromone in the largest state that can induce dauer larva stage due to stress or worsened living environment. And then the inventors isolated and purified the pheromone secreted from the *C. elegans*, and determined the chemical configuration of a purified pheromone. As a result, it has noted that the purified pheromone is 6-(3,5-dihydroxy-6-methyl-tetrahydro-pyran-2-yloxy)heptanoic acid, having a following two-dimensional planar structure formula(Paik et al, Korean Patent Ap-

plication No. 10-2002-0070591 and PCT application No. PCT/KR03/ 02059)

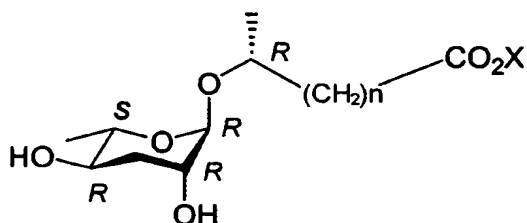


- [6] However, a three-dimensional chemical configuration of the above two-dimensional pheromone compound and a total synthesis are not known yet. Since the novel pheromone compound has 5 asymmetric carbons, the stereochemistry configuration of the pheromone compound may be possibly provided with 36 stereoisomers. Therefore, a stereochemistry configuration should be essentially determined to synthesize the pheromone compound identical with exact natural pheromone having a correct stereochemistry.
- [7] In addition, in order to research aging, stress, metabolism, signal transfer system in vivo, to develop medical substances relating to anticancer, obesity and a suppressing agent for aging and stress, and to research active target protein body of the pheromone, it is inevitably required to develop full synthesis method for mass-production of the pheromone.
- [8] Therefore, the inventors determined a three-dimensional stereochemistry configuration of the pheromone isolated from *C. elegans* to synthesize the pheromone identical with natural pheromone using spectroscopic technologies. In addition, the inventors successfully performed stereospecific total synthesis, thereby obtaining the pheromone fully identical with the natural pheromone. This method provides the mass-production of the pheromone, overcoming the limited amount of natural pheromone. In addition, it is identified that the pheromone obtained according to the present invention has dauer formation effect in vivo test using *C. elegans*.

## Disclosure of Invention

### Technical Solution

- [9] Therefore, it is an object of the present invention to provide a pheromone compound having a stereochemistry formula (I-1).



[10] (I-1)

[11] where, X is hydrogen, alkali or alkali earth metal and n is 1-6 integer.

[12] It is another object of the present invention to provide a method for mass-production of the pheromone with high yield.

[13] It is still another object of the present invention to determine a three-dimensional stereochemistry configuration to accurately synthesize the pheromone.

[14] It is still yet another object of the present invention to provide an intermediate for mass-production of the pheromone with high yield.

[15] It is still yet another object of the present invention to provide a use of a pheromone as medical agent for curing disease relating to aging and stress.

#### Description of Drawings

[16] FIG. 1 is a HR-MS-FMB spectrum of a pheromone of stereochemistry formula (I) according to the present invention;

[17] FIG. 2 is an IR spectrum of the pheromone according to the present invention;

[18] FIG. 3 is a  $^1\text{H}$ -NMR spectrum of the pheromone according to the present invention;

[19] FIG. 4 is a  $^{13}\text{C}$ -NMR spectrum of the pheromone according to the present invention;

[20] FIG. 5 is a  $^{13}\text{C}$ -NMR DEPT spectrum of the pheromone according to the present invention;

[21] FIG. 6 is a 2D-NMR HMBC spectrum of the pheromone according to the present invention;

[22] FIG. 7 is a 2D-NMR HMQC spectrum of the pheromone according to the present invention;

[23] FIG. 8 is a 2D-NMR ROESY spectrum of the pheromone according to the present invention;

[24] FIG. 9 is a 2D-NMR TOCSY spectrum of the pheromone according to the present invention;

[25] FIG. 10 is a 2D-NMR NOE(1) spectrum of the pheromone according to the present invention;

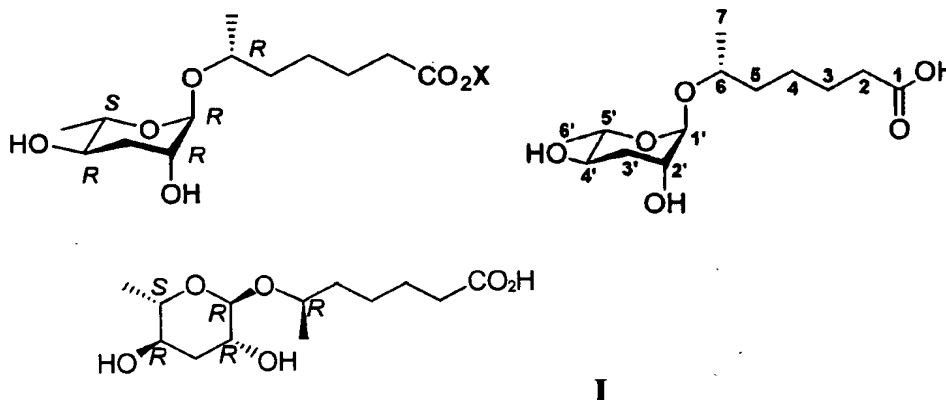
[26] FIG. 11 is a 2D-NMR NOE(2) spectrum of the pheromone according to the present invention;

invention; and

[27] FIG. 12 is a 2D-NMR NOE(3) spectrum of the pheromone according to the present invention.

### Mode for Invention

[28] A three-dimensional stereochemistry formula (I) of 6R-(3,6-dideoxy-L- arabinohexopyranosyloxy)heptanoic acid as a pheromone compound isolated from C. elegans is determined according to spectroscopic analysis such as HR-MASS, IR, DEPT, 2D-NMR(HMBC, HMQC, NOE, ROESY, and TOCSY).



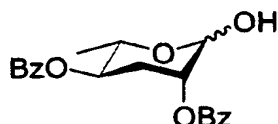
[29] A pure molecular weight of the pheromone, 6R-(3,6-dideoxy-L-arabinohexopyranosyloxy)heptanoic acid, is 276 dalton, and a monocular formula of the pheromone is  $C_{13}H_{24}O_6$ . A calculated high-resolution mass number of the pheromone is 276.1651. It is noted that a high-resolution mass number measured by a high resolution-FAB is 276.1652, and this mass number is almost identical to the calculated mass number (see Fig. 1). Functional groups of relative carbonyl and hydroxy groups of the pheromone molecule are identified by an infrared (IR) analysis (see Fig. 2).

[30] In order to determine the three-dimensional stereochemistry configuration of the novel pheromone compound of formula (I), 2D-proton nuclear magnetic resonance spectrum ( $^1H$ -NMR) is measured by using deutero-methanol ( $CD_3OD$ ) as a solvent. A  $C-13$  nuclear magnetic resonance spectrum ( $^{13}C$ -NMR) is also measured by using deutero-methanol ( $CD_3OD$ ) as a solvent. The chemical shift is represented by ppm.

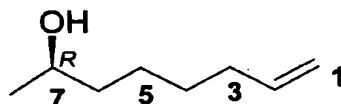
[31] After the location of each carbon is identified by  $^1H$ -NMR (see Fig. 3),  $^{13}C$ -NMR (see Fig. 4) and DEPT (see Fig. 5), the chemical shift of  $^1H$ - and  $^{13}C$ - is measured by using HMBC (see Fig. 6), HMQC (see Fig. 7), ROESY (see Fig. 8), and TOCSY (see Fig. 9) spectrums to identify the accurate relation of the  $^1H$ - and  $^{13}C$ . Table 4 shows a result of HMBC spectrum.

[32] In order to measure the stereo interrelation in the three-dimensional space, the two-dimensional NMR technology of NOE is used. Figs. 10 through 12 show the obtained NOE spectrum.

[33] The 6R-(3,6-dideoxy-L-arabino-hexopyranosyloxy)heptanoic acid of the stereochemistry formula (I) is obtained by a coupling reaction of reactants represented in formulas (II) and (III).



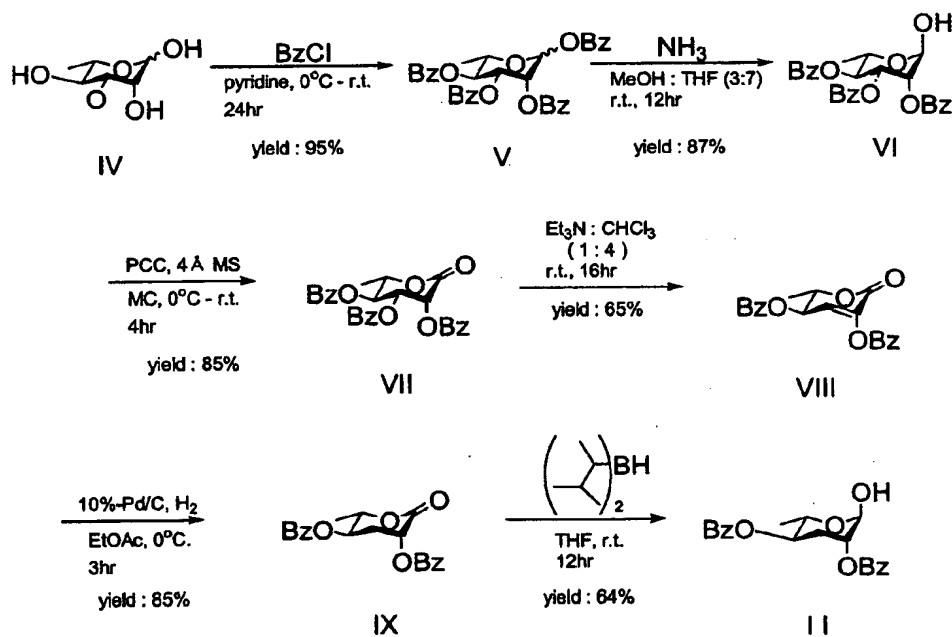
(II)



(III)

[34] 2,4-di-O-benzyl-3,6-dideoxy-L-arabino-hexopyranose of formula (II) is synthesized as shown in the following reaction formula 1 from L-rhamnose monohydrate of formula (IV).

[35] (Reaction Formula 1)



[36] where, Bz is benzyl or benzyl group.

[37] Compound of formula (V) is produced from the compound of formula (IV) by protecting 4 hydroxide groups of the compound (IV) using benzoylchloride.

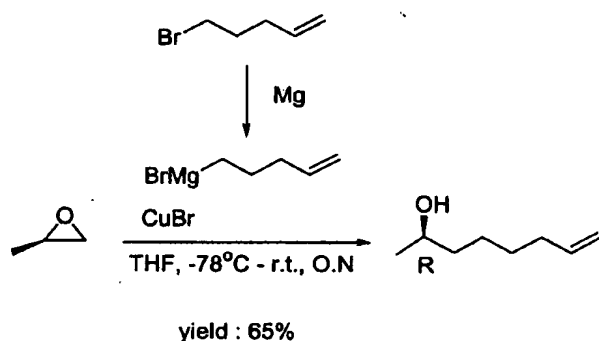
Compound (VI) is produced by selectively eliminating C-1 benzoyl group of the compound (V) using ammonia.

[38] Ketone compound of formula (VII) is produced by oxidizing the C-1 hydroxide group of the compound (VI) using pyridinium chlorochromate (PCC). Compound of formula (VIII) is produced by selectively eliminating C-3 benzoyl group of the compound of formula (VII). Compound of formula (IX) is obtained from the compound of formula (VIII) through hydrogenation in the presence of 10% palladium/carbon catalyst. At this point, the C-2 O-benzoyl group of the compound of formula (IX) has a  $\beta$ -direction.

[39] Finally, by reducing C-1 ketone group of the compound of formula (IX) using chiral diisoamylborohydride,  $\alpha$ -anomer of 2,4-di-O-benzoyl-3,6-dideoxy-L-arabinohexopyranose (II) is produced as a stereospecific C-1 intermediate.

[40] Another reactant, the compound of formula (III) is produced according to following reaction formula 2 from (R)-(+)-1,2-epoxypropane as a raw material.

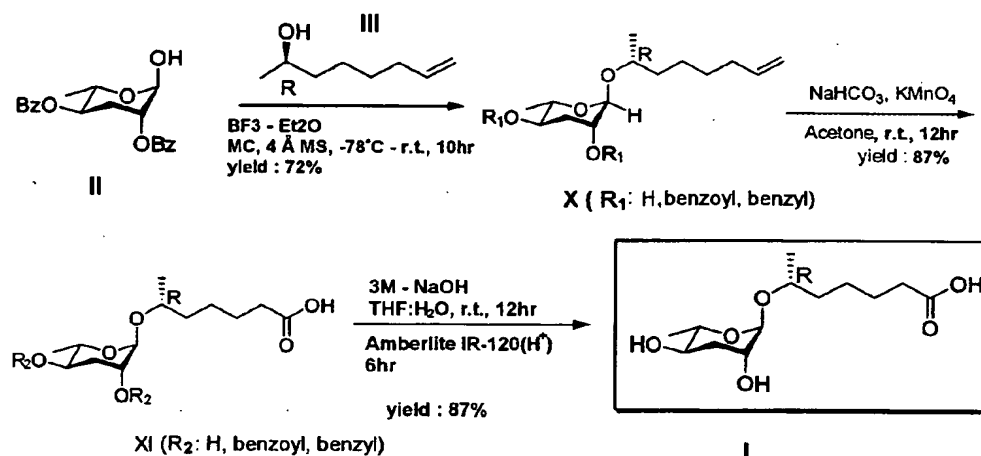
[41] (Reaction Formula 2)



[42] As shown in the reaction formula 2, the (R)-(+)-1,2-epoxypropane is added to separately synthesized 1M 4-pentenyl magnesium bromide, obtaining a (2R)-7-octen-2-ol (III).

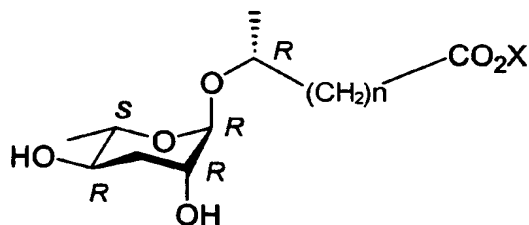
[43] The compound of formula (I) is obtained by reacting the compounds of formulas (II) and (III) through following reaction formula 3.

[44] (Reaction Formula 3)



[45] Coupling compound, (2R)-oct-7-en-2-yl-2,4-di-O-benzyl-3,6-dideoxy-  $\alpha$ -L-arabino-hexopyranoside (X) is obtained through acetalation of the compounds of the formulas (II) and (III) on the presence of Lewis acid catalyst. (6R)-6-(2,4-di-O-benzyl-3,6-dideoxy-  $\alpha$ -L-arabino-hexopyranosyl)heptanoic acid (XI) as an organic acid is produced through a single reaction of terminal aliphatic double bond of the compound of formula (X) using potassium permanganate as an oxidant. Finally, the compound of formula (I) is produced by eliminating C-2 and C-4 benzoyl groups of the compound of formula (XI) by sodium hydroxide and acidifying using amberlite.

[46] In addition, the compound of formula (I) reacts with a base to form addition salts of the compound of formula (I-1). As the base, alkali or alkali earth metal salt that can be pharmaceutically allowed may be used.



[47] (I-1)

[48] where, X is hydrogen, alkali or alkali earth metal and n is 1-6 integer.

[49] It is noted through the spectrometry (2D-NMR, C-13 NMR, IR, HRMS, specific rotation =  $[\alpha]_D^{20} = -81.0$  (c=0.1, MeOH)) that the spectrum of the fully synthetic compound of formula (I) is identical to that of the natural pheromone.

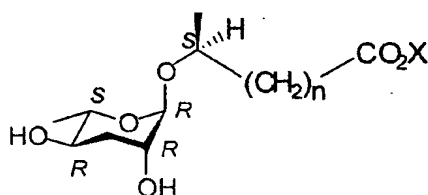
[50] Since the total synthesis starts with L-rhamnose, an absolute stereo configuration of which is well known, and a measured value of all spectrum of the compound of

formula (I) is identical to that of the natural pheromone, it can be noted that the absolute stereoconfiguration of the natural pheromone isolated from the *C. elegans* is the formula (I).

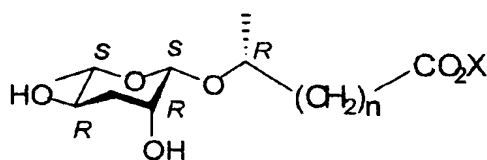
[51] In addition, in the course of the reaction formula 3 synthesis, a variety of derivatives of the formula (I-1) is prepared by coupling other alkyl organic acid having a 1-6 carbon chain, instead of the formula (III).

[52] In addition, in the course of the reaction formula 3 synthesis, when a 7S-stereoisomer of the formula (III) is reacted, 6S stereoisomer (I-2) of the compound (I) can be synthesized.

[53] In the course of preparing the compound of formula (II) from the compound of formula (IX) in the reaction formula 1, when C-1'  $\beta$ -epimer of the compound of formula (II) obtained is used, compound of formula (I-3) having C-1' S stereoisomer can be synthesized.



[54] (I-2)



[55] (I-3)

[56] where, n is 1-6 integer and X is H, alkali or alkali earth metal.

[57] By the above synthesis, the inventive pheromone (I) and the derivatives thereof can be mass-produced. Therefore, it becomes possible to research active target protein body of the pheromone and medical efficacy relating to suppress of aging and stress.

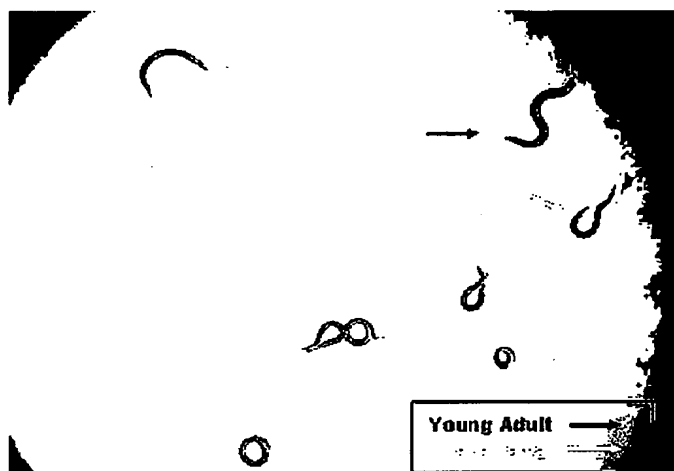
[58] Next, dauer formation effect of the compound of 6R-(3,6-dideoxy-L- arabinohexopyranosyloxy)heptanoic acid (I), which is synthesized according to the present process of the invention, is measured using *C. elegans*.

[59] That is, the dauer formation effect of the synthetic pheromone is measured using *C. elegans* under different feed, temperature and crowd density conditions from each other.

[60] Although it should be passed from an L2 first half step or L3 second half step to an adult step in a condition where the feed and temperature (15-25 °C ) are proper and the crowd density is low, when the synthetic pheromone is mixed, the step goes to dauer larva stage.

[61] The *C. elegans* in the dauer larva does not eat and move, being formed in a circular-shape. For comparison, seven *C. elegans* in the dauer larva and one *C. elegans* in the adult step are comparatively observed. As a result, it is noted that the synthetic pheromone greatly affects the dauer formation effect. In Picture 1, it can be noted that the *C. elegans* is not grown without moving.

[62] Picture 1 Dauer larva and young adult of *C. elegans* after treatment of the synthetic pheromone (I)



[63] Picture 2 shows an image illustrating that the *C. elegans* goes to the dauer larva stage.



[64] Picture 2 *C. elegans* in the Dauer larva

[65] Next, as shown in Table 3, it can be noted that 100% of the dauer formation effect can be obtained when 320  $\mu\text{g}$  /plate of the synthetic pheromone and is used.

[66] Such a result becomes the base for research to be advanced and much amount of the pheromone is required for a variety of searches. Therefore, this shows that the

synthetic pheromone is important. That is, since the synthesis of a large amount of pheromone and a variety of derivatives becomes possible according to the present invention, the more preferable research may be expected.

### DETAILED DESCRIPTION OF THE INVENTION

[67] The present invention will now be described more apparent by describing in detail exemplary embodiments thereof.

[68] **Embodiment 1**

[69] Synthesis of 1,2,3,4-tetra-O-benzoyl-L-rhamnopyranose (V)

[70] L-rhamnose monohydrate (IV) (7.5g, 41.2 mmol) is dissolved in dry pyridine (100 ml), and then benzoylchloride (28.7 ml, 0.247 mmol) is added thereto in a state where the temperature is lowered to 0 °C. The temperature of the reactant is gradually increased to room temperature, and water (15 ml) is added after 16 hours, completing the reaction.

[71] An obtained product is extracted with  $\text{CH}_2\text{Cl}_2$  (50 ml x 2). It is washed by 1M HCl (40 ml x 2) and saturation  $\text{NaHCO}_3$  solution (40 ml) and dried by  $\text{MgSO}_4$ . The solution is vacuum concentrated, and then the compound (V) (22.7g, 95%,  $\alpha : \beta = 2:1$ ) is isolated using flash column chromatography (toluene/EtOAc, 10:1, v/v).

[72] V  $\alpha$ ; an amorphous white solid,  $R_f = 0.58$  (toluene/EtOAc, 10:1, v/v);

[73]  $[\alpha]_D^{22} = +82.0$  ( $c = 1.5$ ,  $\text{CHCl}_3$ ) [lit. 41  $[\alpha]_D = +80.0$  ( $c = 1.5$ ,  $\text{CHCl}_3$ )];

[74] IR(film)  $\text{V}_{\text{max}}$  3066, 3032, 2986, 1730, 1601, 1452, 1260, 1176, 1094, 1068, 1027  $\text{cm}^{-1}$ ;

[75]  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  8.22-7.25 (m, 20H, aromatic H), 6.57 (d, 1H,  $J = 1.6$  Hz H-1), 6.01 (dd, 1H,  $J = 3.4$ , 10.2 Hz H-3), 5.89 (dd, 1H,  $J = 1.9$ , 3.2 Hz H-2), 5.82 (t, 1H,  $J = 10.0$  Hz H-4), 4.41-4.35 (m, 1H, H-5), 1.42 (d, 3H,  $J = 6.2$  Hz -CH<sub>3</sub>);

[76]  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ )  $\delta$  165.8(2), 165.4, 164.1, 134.0, 133.8, 133.6, 133.4, 130.2(2), 130.1(2), 129.8(4), 129.1(2), 129.0(2), 128.8(2), 128.7(2), 128.6(2), 128.4(2), 91.4(C-1,  $\alpha$ ), 71.3, 70.0, 69.8, 69.4, 17.8(C-6);

[77] An HRMS(FAB) calculated value for  $\text{C}_{34}\text{H}_{28}\text{NaO}_9$  ( $\text{M}^+ + \text{Na}$ )  $m/z$  is 603.1631, an actual measured value is 603.1637

[78] **Embodiment 2**

[79] Synthesis of 2,3,4-tri-O-benzoyl-L-rhamnopyranose (VI)

[80] The compound (V) (22.4g, 38.6 mmol) is dissolved in MeOH:THF (3:7, 400 ml) and then  $\text{NH}_3$  gas is bubbled for 15 minutes at 0 °C and stirred at 0 °C for 1 hour. The reaction process is identified by thin layer chromatography while repeating the above process. The solvent is vacuum concentrated, and then the compound (VI) (16g, 87%)

$\alpha : \beta = 14:1$ ) is isolated using flash column chromatography (toluene/EtOAc, 10:1, v/v).

[81] VI  $\alpha$  ; a white solid, Rf=0.18 (toluene/EtOAc, 10:1, v/v);

[82]  $[\alpha]_D^{23} = +236.0$  (c = 1.0, CHCl<sub>3</sub>);

[83] IR(film) Vmax 3458, 3062, 2985, 2935, 1727, 1601, 1451, 1348, 1264, 1102, 1069, 1027 cm<sup>-1</sup>;

[84] <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  8.12-7.22 (m, 15H, aromatic H), 5.95 (dd, 1H, J = 3.2, 10.1 Hz H-3), 5.74-5.62 (m, 2H), 5.49-5.48 (m, 1H), 4.54-4.43 (m, 1H, H-5), 4.21 (d, 1H, J = 4.0 Hz -OH), 1.37 (d, 3H, J = 6.2 Hz -CH<sub>3</sub>);

[85] <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>)  $\delta$  166.0, 165.9, 165.8, 133.6, 133.5, 133.3, 130.0(2), 129.9(2), 129.8(2), 129.4, 129.3, 129.2, 128.7(2), 128.5(2), 128.4(2), 92.3(C-1,  $\alpha$ ), 72.1, 71.5, 69.9, 66.7, 17.8(C-6);

[86] An HRMS(FAB) calculated value for C<sub>27</sub>H<sub>24</sub>NaO<sub>8</sub> (M<sup>+</sup> + Na) m/z is 488.1369, and an actual measured value is 499.1372.

[87] **Embodiment 3**

[88] Synthesis of 2,3,4-tri-O-benzoyl-L-rhamnono-1,5-lactone (VII)

[89] PCC (30 g, 0.139 mmol) and well-dried 4 ? molecular sieves (25 g) are added into a flask under N<sub>2</sub> current. Dry CH<sub>2</sub>Cl<sub>2</sub> (250 mL) is added to the flask and the flask is stirred for 1 hour at a room temperature and cooled to 0 °C. The compound (VI) (16 g, 33.6 mmol) dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (250 mL) is added to and stirred 4 hours at a room temperature. The reaction is finished with adding cool Et<sub>2</sub>O (200 mL) and filtered by silica gel. The solvent is vacuum concentrated, and then the compound (VII) (13.54g, 85%) is isolated using flash column chromatography (toluene/EtOAc, 10:1, v/v).

[90] VII; an amorphous white solid, Rf=0.51 (toluene/EtOAc, 10:1, v/v);

[91]  $[\alpha]_D^{22} = -10.0$  (c = 0.5, CHCl<sub>3</sub>);

[92] IR(film) Vmax 3064, 3031, 2983, 2936, 1784, 1730, 1601, 1452, 1393, 1259, 1096, 1026 cm<sup>-1</sup>;

[93] <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  8.10-7.29 (m, 15H, aromatic H), 6.28 (d, 1H, J = 3.8 Hz), 6.05 (dd, 1H, J = 1.4, 3.8 Hz), 5.34 (dd, 1H, J = 1.4, 11.0 Hz), 4.96-4.85 (m, 1H, H-5), 1.61 (d, 3H, J = 6.3 Hz -CH<sub>3</sub>);

[94] <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>)  $\delta$  165.9(C-1), 165.1, 164.9, 164.8, 134.0, 133.9, 133.8, 130.1(4), 130.0(2), 128.7(5), 128.5(3), 128.4, 74.8, 74.1, 71.8, 67.6, 19.0(C-6);

[95] An HRMS(FAB) calculated value for C<sub>27</sub>H<sub>23</sub>O<sub>8</sub> (M<sup>+</sup> + H) m/z is 475.1393, and an actual measured value is 475.1393.

[96] **Embodiment 4**

- [97] Synthesis of 2,4-di-O-benzoyl-3,6-dideoxy-L-erythro-hex-2-enono-1,5-lactone (VIII)
- [98] The compound (VII) (13.2 g, 27.8 mmol) is dissolved in Et<sub>3</sub>NCHCl<sub>3</sub> (1:4, 500 mL) under N<sub>2</sub> current and stirred for 16 hours at a room temperature. After the reaction is finished, it is washed by water. An organic layer is dried using anhydrous MgSO<sub>4</sub>. The solution is vacuum concentrated and then the compound (VIII) (6.37g, 65%) is isolated using flash column chromatography (toluene/EtOAc, 10:1, v/v).
- [99] VIII; a crystalline white solid, R<sub>f</sub>=0.53 (toluene/EtOAc, 10:1, v/v);
- [100] mp 108-112 °C (lit.<sup>40</sup> mp 107-110 °C);
- [101] [α]<sub>D</sub><sup>21</sup> = -93.1 (c = 1.0, CHCl<sub>3</sub>) [lit.<sup>43</sup> [α]<sub>D</sub><sup>20</sup> = -93.0 (c = 1.0, CHCl<sub>3</sub>)];
- [102] IR(film) V<sub>max</sub> 3069, 3007, 2936, 2920, 1738, 1674, 1598, 1452, 1355, 1257, 1155, 1115, 1060 cm<sup>-1</sup>;
- [103] <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 8.13-7.44 (m, 10H, aromatic H), 6.71 (d, 1H, J = 4.3 Hz H-3), 5.69 (t, 1H, J = 4.7 Hz H-4), 5.00-4.90 (m, 1H, H-5), 1.64 (d, 3H, J = 6.7 Hz -CH<sub>3</sub>);
- [104] <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>) δ 165.5, 164.3, 158.0(C-2), 140.8, 134.3, 133.9, 130.5(2), 130.0(2), 128.7(5), 127.9, 125.6, 77.4, 68.6, 18.4(C-6);
- [105] An HRMS(FAB) calculated value for C<sub>20</sub>H<sub>17</sub>O<sub>6</sub> (M<sup>+</sup> + H) m/z is 353.1025, and an actual measured value is 353.1023.
- [106] **Embodiment 5**
- [107] Synthesis of 2,4-di-O-benzoyl-3,6-dideoxy-L-arabino-hexono-1,5-lactone (IX)
- [108] The compound (VIII) (6.1 g, 17.31 mmol) is dissolved in EtOAc (300 mL) and then 10%-Pd/C (400 mg) is added and is stirred for 3 hours at a room temperature after being substituted with hydrogen gas. The reactant is filtered by using celite 545. The solution is vacuum concentrated and then the compound (IX) (5.2g, 85%) is isolated using flash column chromatography (toluene/EtOAc, 10:1, v/v).
- [109] IX; a white solid, R<sub>f</sub>=0.45 (toluene/EtOAc, 10:1, v/v);
- [110] [α]<sub>D</sub><sup>21</sup> = +18.4 (c = 1.0, CHCl<sub>3</sub>) [lit.<sup>43</sup> [α]<sub>D</sub><sup>20</sup> = +18.2 (c = 1.0, CHCl<sub>3</sub>)];
- [111] IR(film) V<sub>max</sub> 3031, 2982, 2939, 1724, 1601, 1452, 1383, 1273, 1114, 1070, 1028 cm<sup>-1</sup>;
- [112] <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 8.11-7.43 (m, 10H, aromatic H), 5.90 (dd, 1H, J = 7.6, 12.0 Hz H-2), 5.30-5.25 (m, 1H, H-4), 4.87-4.77 (m, 1H, H-5), 2.78-2.52 (m, 2H, H-3eq, 3ax), 1.58 (d, 3H, J = 6.5 Hz -CH<sub>3</sub>);
- [113] <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>) δ 168.0(C-1), 165.5(2), 133.9, 133.8, 130.2(2), 129.9(2), 129.1, 129.0, 128.8(2), 128.6(2), 76.9, 70.5, 65.0, 30.2(C-3), 19.3(C-6).

- [114] An HRMS(FAB) calculated value for  $C_{20}H_{19}O_6$  ( $M^+ + H$ )  $m/z$  is 355.1182, and an actual measured value is 355.1178.
- [115] **Embodiment 6**
- [116] Synthesis of 2,4-di-O-benzoyl-3,6-dideoxy-L-arabino-hexopyranose (II)
- [117] (1) Preparation of 0.5M Diisoamylborohydride
- [118] 1M  $BH_3$ -THF (65 ml) is cooled to  $-10^\circ C$  under  $N_2$  current, and then 2M 2,3-dimethyl-2-butene (65 ml) is gradually added. It is stirred for 2 hours at  $0^\circ C$  and used in the reaction (2).
- [119] (2) Synthesis of 2,4-di-O-benzoyl-3,6-dideoxy-L-arabino-hexopyranose (II)
- [120] The compound (IX) (5g, 14.11 mmol) dissolved in dry THF (15 ml) is added to 0.5M Diisoamylborohydride (127 ml) prepared in the reaction (1). Then, it is stirred for 20 hours at a room temperature. After the reaction is finished, water (3 ml) is added and then stirred for 30 minutes. The reaction mixture is cooled to  $0^\circ C$ , and then 30%  $H_2O_2$  (15 ml) is added and 3N NaOH is added to maintain the pH 7-8. The solvent THF is vacuum concentrated, and then it is dissolved in  $CH_2Cl_2$  (100 ml) and washed by water (50 ml). An organic layer is dried using anhydrous  $MgSO_4$ . The solution is vacuum concentrated, and then the compound (II) (4.72g, 93.8%,  $\alpha : \beta = 4.6:1$ ) is isolated using flash column chromatography (toluene/EtOAc, 10:1, v/v).
- [121] II  $\alpha$ ; a colorless syrup,  $R_f=0.23$  (toluene/EtOAc, 10:1, v/v);
- [122]  $[\alpha]_D^{24} = +51.4$  ( $c = 1.0$ ,  $CHCl_3$ );
- [123] IR(film)  $V_{max}$  3448, 3065, 3027, 2979, 1720, 1601, 1452, 1270, 1112, 1095, 1068, 1025  $cm^{-1}$ ;
- [124]  $^1H$  NMR (250 MHz,  $CDCl_3$ )  $\delta$  8.15-7.43 (m, 10H, aromatic H), 5.29 (s, 1H, H-1), 5.25-5.15 (m, 2H, H-2, H-4), 4.39-4.28 (m, 1H, H-5), 3.51 (d, 1H,  $J = 3.6$  Hz, OH), 2.44 (td, 1H,  $J = 3.8, 13.5$  Hz, H-3eq), 2.29 (ddd, 1H,  $J = 3.1, 11.0, 13.7$  Hz, H-3ax), 1.30 (d, 3H,  $J = 6.2$  Hz,  $-CH_3$ );
- [125]  $^{13}C$  NMR (62.9 MHz,  $CDCl_3$ )  $\delta$  166.0, 165.8, 133.5, 133.4, 130.0(3), 129.8(3), 128.6(4), 91.1(C-1,  $\alpha$ ), 71.0(C-2), 70.7(C-4), 67.0(C-5), 29.2(C-3), 18.0(C-6).
- [126] An HRMS(FAB) calculated value for  $C_{20}H_{21}O_6$  ( $M^+ + H$ )  $m/z$  is 357.1338, and an actual measured value is 357.1334.
- [127] **Embodiment 7**
- [128] Synthesis of (2R)-7-Octene-2-ol (III)
- [129] (1) Synthesis of 4-pentenylmagnesium bromide
- [130] 5-bromo-1-pentene (2.8 ml, 23.5 mmol) dissolved in dry THF (20 ml) is added to Mg suspension (571 mg, 23.5 mmol) dissolved in dry THF (3 ml) dropwise for over

30 minutes. The reaction mixture is refluxed for 3 hours at 60 °C, after which it is cooled to a room temperature, thereby preparing Grignard solution.

[131] (2) Synthesis of (2R)-7-Octene-2-ol (III)

[132] (R)-(+)-1,2-epoxypropane (1.12 mL, 16.0 mmol) is dissolved in dry THF (23 mL) and CuBr (230 mg, 1.6 mmol) is added therein; after which the temperature is reduced to -78 °C. The 1M 4-pentenylmagnesium bromide solution (23 mL, 23.5 mmol) prepared in the reaction (1) is added to reaction mixture. The temperature is gradually increased to a room temperature and the mixture is stirred for 4 hours. The reaction is finished with saturated NH<sub>4</sub>Cl solution (10 mL). An obtained product is extracted with Et<sub>2</sub>O (20 mL X 2) and it is washed by water (10 mL). An organic layer is dried using anhydrous MgSO<sub>4</sub>. The solution is vacuum concentrated, and then the compound (III) (1.3g, 65%) is isolated using flash column chromatography (Et<sub>2</sub>O/n-pentene, 5:1, v/v).

[133] III; a colorless liquid, R<sub>f</sub>=0.15 (Et<sub>2</sub>O/n-pentene, 5:1, v/v);

[134] [α]<sub>D</sub><sup>23</sup> = -10.7 (c = 0.28, CHCl<sub>3</sub>);

[135] IR(film) V<sub>max</sub> 3357, 2969, 2930, 2858, 1641, 1460, 1416, 1374, 1305, 1122 cm<sup>-1</sup>

[136] <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 5.89-5.73 (m, 1H, H-2), 5.03-4.92 (m, 2H, H-1), 3.80-3.78 (m, 1H, H-7), 2.07 (m, 2H, H-3), 1.43-1.39 (m, 6H, H-4, 5, 6), 1.18 (d, 3H, J = 6.1 Hz, -CH<sub>3</sub>);

[137] <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>) δ 138.9(C-2), 114.4(C-1), 68.0(C-7), 39.2(C-6), 33.8(C-3), 29.0(C-4), 25.3(C-5), 23.5(C-8)

[138] **Embodiment 8**

[139] Synthesis of (2R)-Oct-7-en-2-yl-2,4-di-O-benzyl-3,6-dideoxy-α-L-arabino-hexopyranoside (X)

[140] The compound(II) (2.0 g, 5.61 mmol, 1eq), the compound(III) (1/08g, 8.42 mmol) and 4 ? molecular sieves (200 g) are dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (30 mL) under N<sub>2</sub> current; after which the temperature is cooled to 0 °C. BF<sub>3</sub>·Et<sub>2</sub>O (2.85 mL, 16.8 mmol, 4eq) is gradually added and stirred for 10 hours; after which Et<sub>3</sub>N (5 mL) is added, and the reaction is finished and filtered. The solution is vacuum concentrated, and then the compound (X) (1.89g, 72%) is isolated using flash column chromatography (n-hexane/EtOAc, 5:1, v/v).

[141] VII; a colorless syrup, R<sub>f</sub>=0.55 (n-hexane/EtOAc, 5:1, v/v);

[142] [α]<sub>D</sub><sup>22</sup> = +0.9 (c = 1.0, CHCl<sub>3</sub>);

[143] IR(film) V<sub>max</sub> 3069, 2974, 2933, 2859, 1723, 1602, 1451, 1316, 1267, 1152, 1108, 1068, 1025 cm<sup>-1</sup>;

[144] <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 8.14-7.42 (m, 10H, aromatic H), 5.93-5.76 (m, 1H);

- 5.26-5.16 (m, 2H, H-2, H-4), 5.07-5.00 (m, 3H, H-1), 4.20-4.09 (m, 1H, H-5), 3.85 (m, 1H), 2.48-2.41 (m, 1H, H-3'eq), 2.28-2.17 (m, 1H, H-3'ax), 2.11 (m, 2H), 1.68-1.37 (m, 6H), 1.30 (d, 3H, J = 6.2 Hz), 1.20 (d, 3H, J = 6.1 Hz);
- [145]  $^{13}\text{C}$  NMR (62.9 MHz  $\text{CDCl}_3$ )  $\delta$  165.9, 165.7, 138.9, 133.3, 133.2, 129.9(3), 129.6(2), 128.5(4), 114.5, 93.8(C-1',  $\alpha$ ), 72.5, 71.3, 70.7, 67.0, 37.0, 33.8, 29.8, 28.8, 25.3, 19.2, 17.9;
- [146] An HRMS(FAB) calculated value for  $\text{C}_{28}\text{H}_{35}\text{O}_6$  ( $\text{M}^+ + \text{H}$ )  $m/z$  is 467.2434, and an actual measured value is 467.2438.
- [147] **Embodiment 9**
- [148] Synthesis of (6R)-6-(2,4-di-O-benzoyl-3,6-dideoxy- $\alpha$ -L-arabino-hexopyranosyl)heptanoic acid (XI)
- [149] The compound(X) (1.8 g, 3.86 mmol) is dissolved in acetone and then  $\text{NaHCO}_3$  (972 mg, 11.57 mmol) is added to therein. Then,  $\text{KNO}_3$  (3g, 19.29 mmol) is gradually added and it is stirred for 12 hours. After the reaction is finished, it is acidified using 10% HCl (20 ml). An obtained product is extracted with EtOAc (100 ml  $\times$  2) and is washed by brine (70 ml). An organic layer is dried by anhydrous  $\text{MgSO}_4$ . The solution is vacuum concentrated, and then the compound (XI) (1.51g, 87%) is isolated using flash column chromatography (n-hexane/EtOAc, 5:1, v/v).
- [150] XI; a colorless syrup,  $R_f=0.13$  (hexane/EtOAc, 5:1, v/v);
- [151]  $[\alpha]_D^{22} = -1.9$  (c = 1.0,  $\text{CHCl}_3$ );
- [152] IR(film)  $\text{V}_{\text{max}}$  3063, 2973, 2935, 1721, 1602, 1451, 1316, 1267, 1109, 1068, 1025  $\text{cm}^{-1}$ ;
- [153]  $^1\text{H}$  NMR (250 MHz  $\text{CDCl}_3$ )  $\delta$  10.69 (bs, 1H, -OH), 8.14-7.42 (m, 10H, aromatic H), 5.26-5.17 (m, 2H, H-2', H-4'), 4.98 (s, 1H, H-1'), 4.19-4.08 (m, 1H, H-5'), 3.87 (m, 1H), 2.47-2.36 (m, 3H), 2.28-2.17 (m, 1H, H-3'ax), 1.72-1.45 (m, 6H), 1.31 (d, 3H, J = 6.2 Hz), 1.21 (d, 3H, J = 6.0 Hz);
- [154]  $^{13}\text{C}$  NMR (62.9 MHz  $\text{CDCl}_3$ )  $\delta$  179.8, 165.8, 165.7, 133.3, 133.2, 130.0, 129.9(2), 129.8, 129.7(2), 128.5(4), 93.8(C-1',  $\alpha$ ), 72.4, 71.2, 70.7, 67.1, 36.7, 34.0, 29.7, 25.2, 24.6, 19.1, 17.9;
- [155] An HRMS(FAB) calculated value for  $\text{C}_{27}\text{H}_{33}\text{O}_8$  ( $\text{M}^+ + \text{H}$ )  $m/z$  is 485.2175, and an actual measured value is 485.2165.
- [156] **Embodiment 10**
- [157] Synthesis of 6R-(3,6-dideoxy-L-arabino-hexopyranosyloxy)heptanoic acid (I)
- [158] The compound(XI) (472.9 mg, 0.976 mmol) is dissolved in MeOH (20 ml).  $\text{NaOMe}$  (52.7 mg, 0.976 mmol) is added at 0 °C. The temperature is gradually increased to a

room temperature and the mixture is stirred for 12 hours. After the reaction is finished, MeOH is vacuum concentrated. Then, in order to eliminate a sub-product methylbenzoate, it is dissolved in water (20 mL) and washed by  $\text{CH}_2\text{Cl}_2$  (20 mL  $\times$  5). The pH of the solution layer is adjusted using amberlite IR-120( $\text{H}^+$ ) (500 mg). After the filtration, the water is removed from the solution layer by freeze drying method, and then the compound (I) (234.6 mg, 87%) is isolated using flash column chromatography (EtOAc/MeOH, 11:1, v/v).

[159] I; a colorless oil,  $R_f=0.43$  (EtOAc/MeOH, 11:1, v/v);

[160]  $[\alpha]_D^{20} = -81.0$  ( $c = 0.1$ , MeOH);

[161] IR(film)  $\text{Vmax}$  3391, 2969, 2933, 1712, 1452, 1379, 1244, 1126, 1103, 1042, 1031  $\text{cm}^{-1}$ ;

[162]  $^1\text{H}$  NMR (500 MHz  $\text{CD}_3\text{OD}$ )  $\delta$  4.64 (s, 1H, H-1'), 3.80-3.77 (m, 1H, H-6), 3.72-3.71 (m, 1H, H-2'), 3.63-3.59 (m, 1H, H-5'), 3.54-3.49 (m, 1H, H-4'), 2.30 (t, 2H,  $J = 7.5$  Hz H-2), 1.96-1.92 (m, 1H, H-3'eq), 1.79-1.74 (m, 1H, H-3'ax), 1.61 (m, 2H, H-3), 1.56-1.50 (m, 2H, H-5), 1.47 (m, 2H, H-4), 1.21 (d, 3H,  $J = 6.5$  Hz H-6'), 1.12 (d, 3H,  $J = 6.5$  Hz H-7);

[163]  $^{13}\text{C}$  NMR (125.7 MHz  $\text{CD}_3\text{OD}$ )  $\delta$  177.7(C-1), 97.6(C-1',  $\alpha$ ), 72.4(C-6), 71.3(C-5'), 70.1(C-2'), 68.5(C-4'), 38.2(C-5), 36.1(C-3'), 35.0(C-2), 26.5(C-3), 26.1(C-4), 19.4(C-7), 18.2(C-6');

[164] An HRMS(FAB) calculated value for  $\text{C}_{13}\text{H}_{25}\text{O}_6$  ( $M^+ + \text{H}$ )  $m/z$  is 277.1651, and an actual measured value is 277.1652.

[165] **Embodiment 11**

[166] Synthesis of base addition salts (I-1:  $n=4$ ,  $X=\text{Na}$ ) of 6R-(3,6-dideoxy-L-arabino-hexopyranosyloxy)heptanoic acid (I)

[167] The compound (I) (267 mg, 1.0 mmol) is dissolved in MeOH (10 mL). NaOMe (40.0 mg, 1.0 mmol) is added at 0 °C. Then, the temperature is gradually increased to a room temperature and the mixture is stirred for 1 hour. After the reaction is finished, MeOH is vacuum concentrated and filtered. Then, the water is removed from a solution layer by freeze drying method, and the compound (I-1) (271 mg, 95%) is isolated.

[168] **Test Example**

[169] Measurement of dauer formation effect activity

[170] To identify the dauer formation effect of the inventive pheromone, an activity is measured after the pheromone compound is supplied to S. basal agar culture medium without peptone (Vowels and Thomas, Genetics 130: 105-123, 1992).

[171] The dauer formation effect activity of the inventive compound with respect to *C. elegans* is shown as Table 3.

[172] Table 3 (Dauer formation effect activity of the pheromone of *C. elegans*)

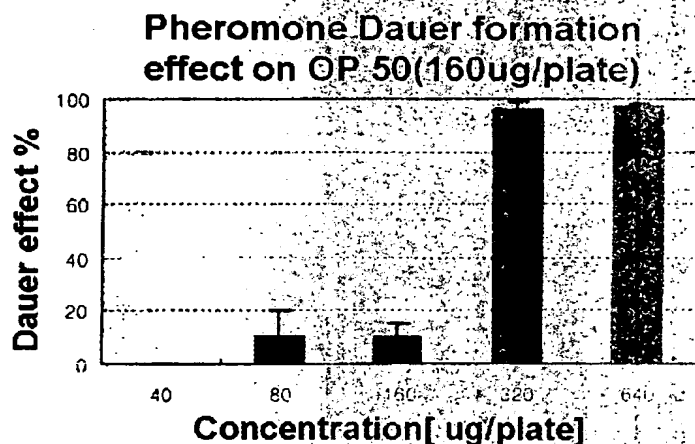


Table 4 (Spectrum analysis result of pheromone, 6R-(3,6-dideoxy-L- arabinohexopyranosyloxy)heptanoic acid

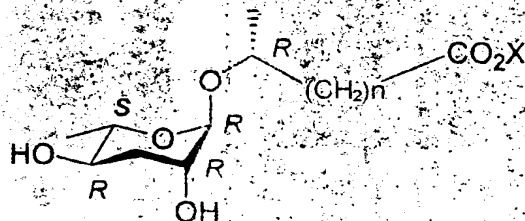
Position	$\delta_H$ (mult, J)	$\delta_C$	HMBC (H to C)
1		177.3	2, 3
2	2.30 (t,7.5)	34.6	1, 3
3	1.64 (m)	25.5	2, 4, 5, 6
4	1.47 (m)	25.1	2, 3, 5
5	1.50-1.48 (m)	37.1	3, 4, 6, 7
6	3.80-3.77 (m)	71.3	5, 7, 1'
7	1.14 (d,6.5)	18.3	5, 6
1'	4.66 (s)	96.6	2', 3', 6
2'	3.73-3.72 (m)	69.0	1', 3'
3'	1.97-1.95 (m)	34.9	1', 4', 5'
	1.79-1.74 (m)		
4'	3.54-3.59 (m)	67.4	3', 5', 6'
5'	3.64-3.62 (m)	70.2	3', 4', 6'
6'	1.24 (d,6.5)	17.2	4', 5'

### Industrial Applicability

- [173] As described above, the present invention firstly determined stereochemistry configuration of pheromone, (6R)-6-(3,6-dideoxy-L-arabino-hexopyranosyloxy) heptanoic acid and salts thereof. Based on this fact, the effective total synthesis was successfully performed, thereby overcoming the minute isolation of the pheromone obtained from *C. elegans* to make it possible to mass-produce the pheromone.
- [174] Accordingly, it becomes possible to develop medical substances using the pheromone relating to aging, stress, metabolism, signal transfer system in vivo, and anti-cancer, obesity and a suppressing agent for aging and stress. In addition, it becomes also possible to research the active target protein body of the pheromone.
- [175] While the present invention has been particularly shown and described with reference to exemplary embodiments thereof, it will be understood by those of ordinary skill in the art that various changes in form and details may be made therein without departing from the spirit and scope of the present invention as defined by the following claims.

## Claims

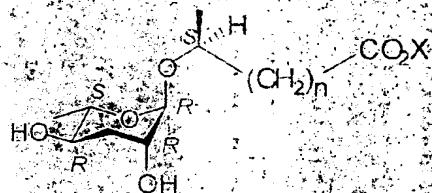
- [1] A pheromone compound having a stereochemistry formula (I-1)



(I-1)

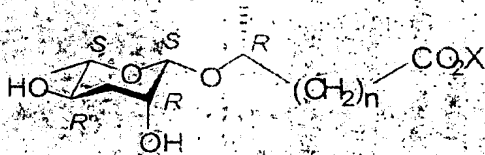
where, X' is H, alkali or alkali earth metal and n is 1-6 integer.

- [2] The pheromone compound of claim 1, wherein the compound of formula (I-1) is 6R-(3,6-dideoxy-L-arabino-hexopyranosyloxy)heptanoic acid.
- [3] The pheromone compound of claim 1, wherein the compound of formula (I-1) is alkali or alkali earth metal salt of 6R-(3,6-dideoxy-L-arabino-hexopyranosyloxy)heptanoic acid.
- [4] The pheromone compound of claim 1, wherein the compound of formula (I-1) is S-form stereoisomer having a stereochemistry formula (I-2).



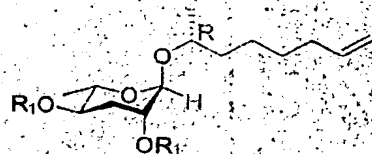
(I-2)

- [5] The pheromone compound of claim 1, wherein the compound of formula (I-1) is C-1' S-form stereoisomer having a stereochemistry formula (I-3).



(I-3)

- [6] A pheromone intermediate having a formula (X).

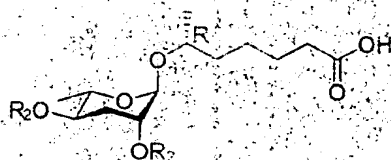


(X)

where, R is H, benzoyl or benzyl group.

[7]

A pheromone intermediate having a formula (XI).

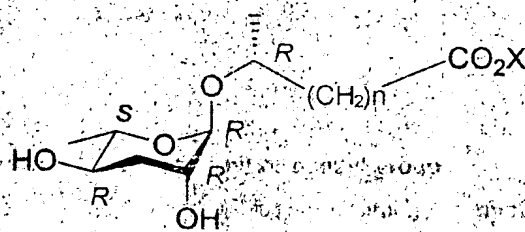


(XI)

where, R is H, benzoyl or benzyl group.

[8]

A preparation method for a pheromone compound having a stereochemistry formula(I-1), the method comprising the steps of:  
 acetalation of compound of formula (II) with compound of formula (III) in the presence of Lewis acid catalyst;  
 converting an aliphatic terminal double bond of produced coupling reactant to an organic acid by an oxidant; and  
 removing two O-benzoyl protecting group of deoxyrihannosyl group by a base and acidifying by a acid.

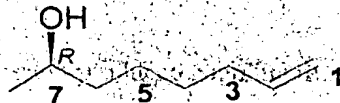


(I-1)



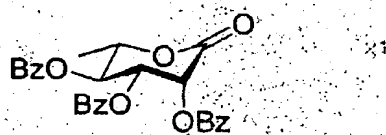
(II)

(III)



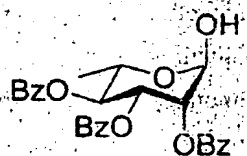
where, Bz is benzyl or benzyl group.

- [9] The preparation method of claim 8, wherein the catalyst is  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  and molecular sieves.
- [10] The preparation method of claim 8, wherein the oxidant is  $\text{KMnO}_4$  and  $\text{NaHCO}_3$  is used as a supplement agent.
- [11] The preparation method of claim 8, wherein the base is of  $\text{NaOH}$  or  $\text{KOH}$  and the acid is amberlite resin type acid.
- [12] The preparation method of claim 8, wherein the compound of formula (II) is obtained from compound of formula (VII).



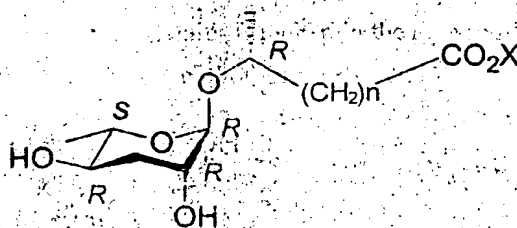
(VII)

- [13] The method of claim 12, wherein the compound of formula (VII) is obtained by oxidating compound of formula (VI).



(VI)

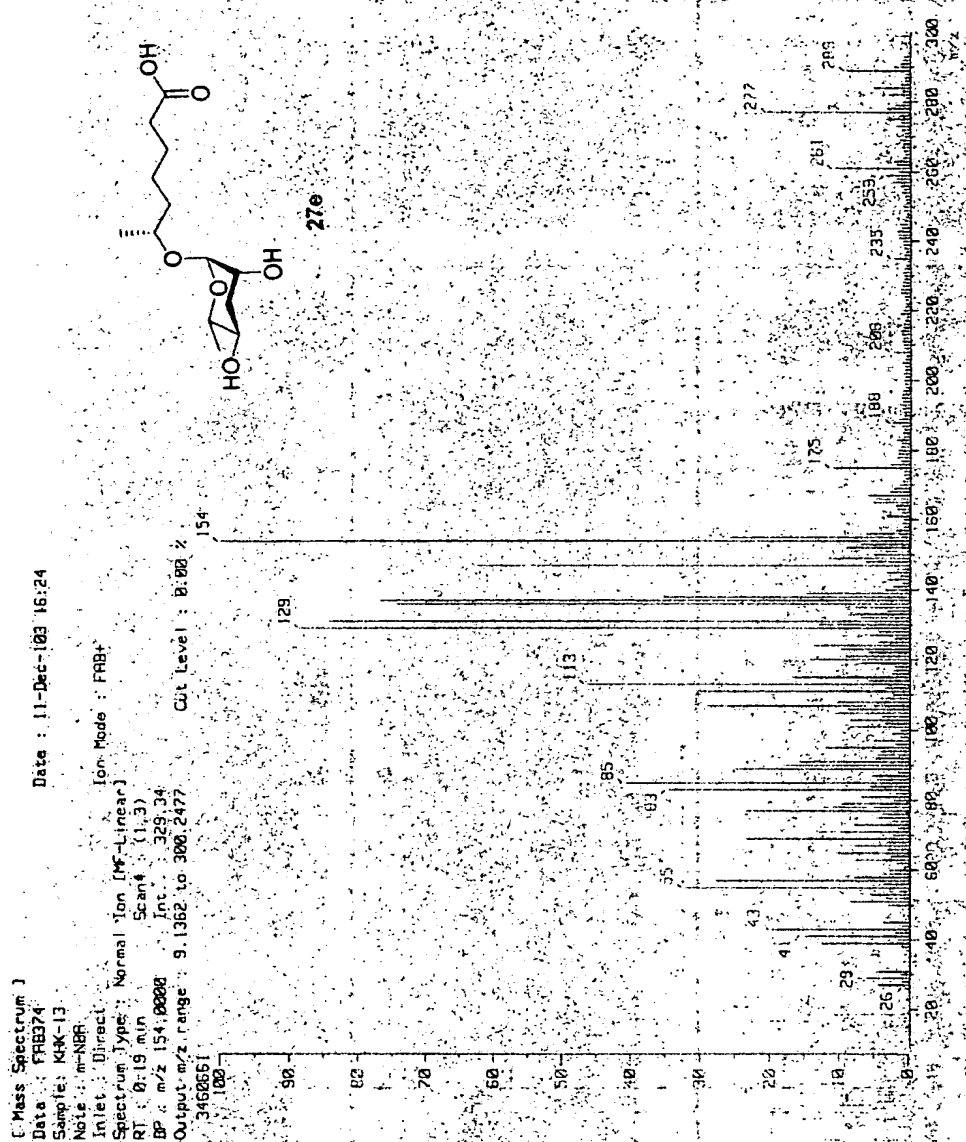
- [14] A use of a pheromone compound of 6R-(3,6-dideoxy-L-arabino-hexopyranosyloxy)-heptanoic acid having a stereochemistry formula (I-1) and its alkali and alkali earth metal salts as medical agent for curing disease relating to aging and stress.



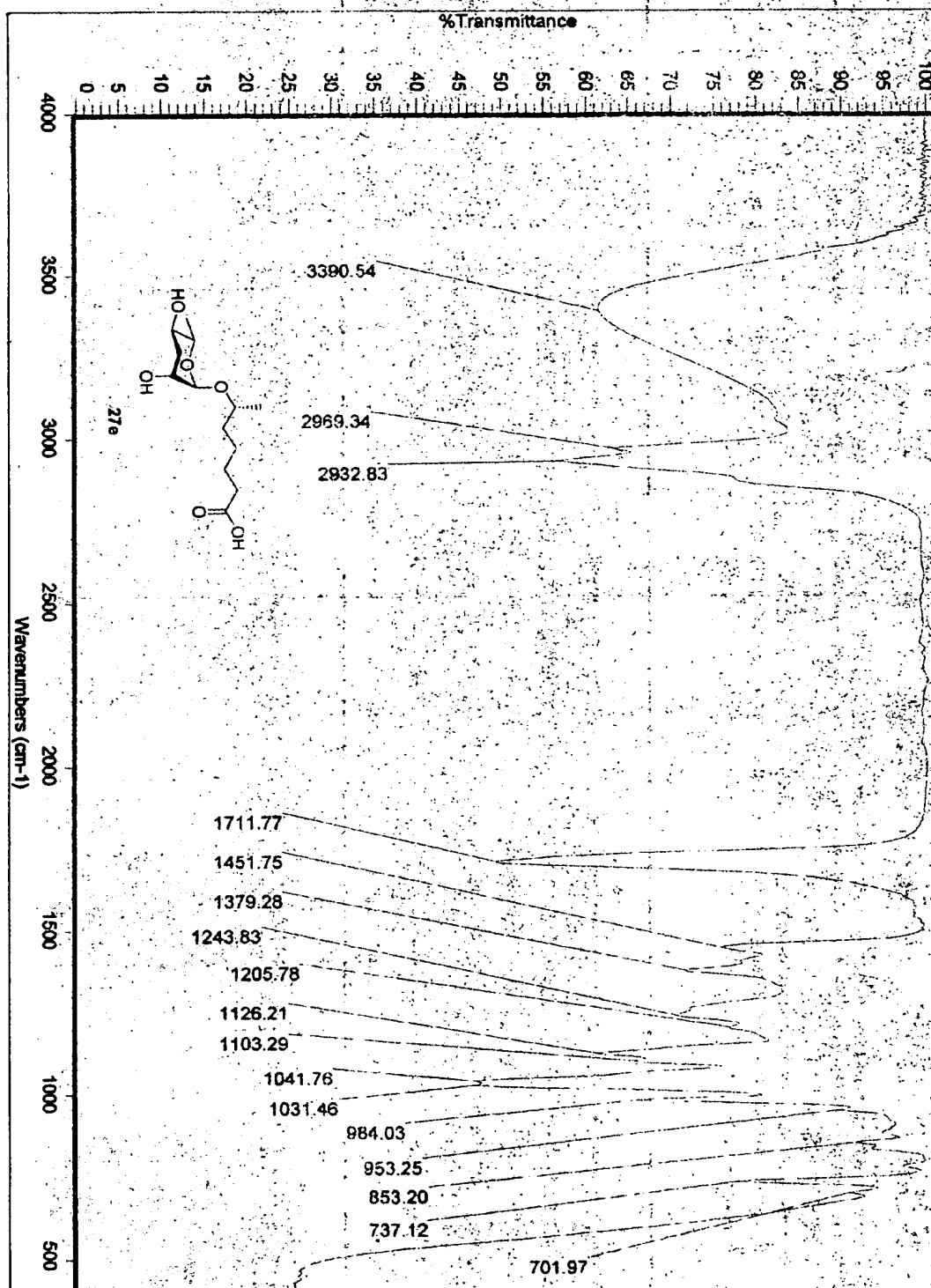
(I-1)

where, X is H, alkali or alkali earth metal and n is 1-6 integer.

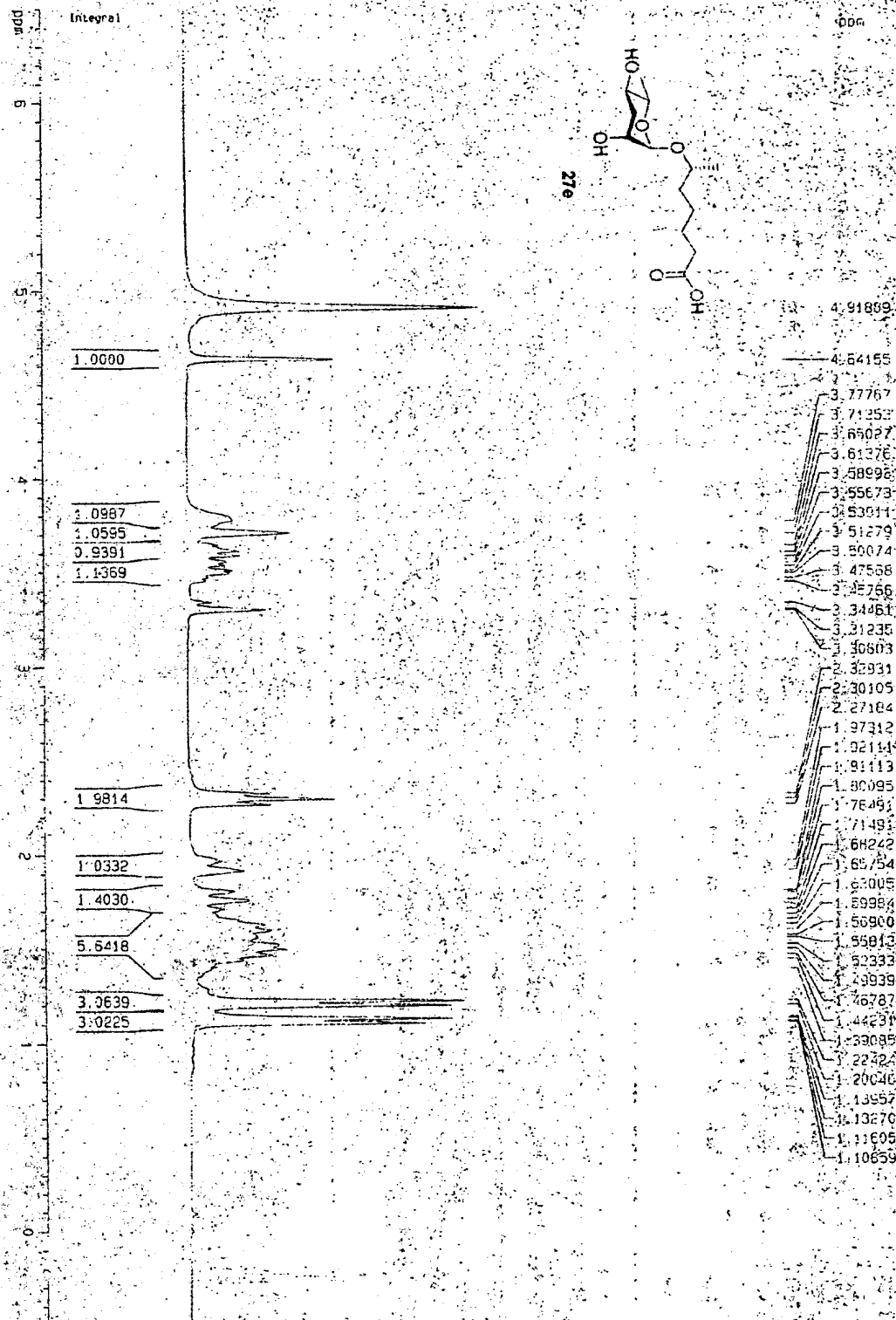
[Fig. 1]



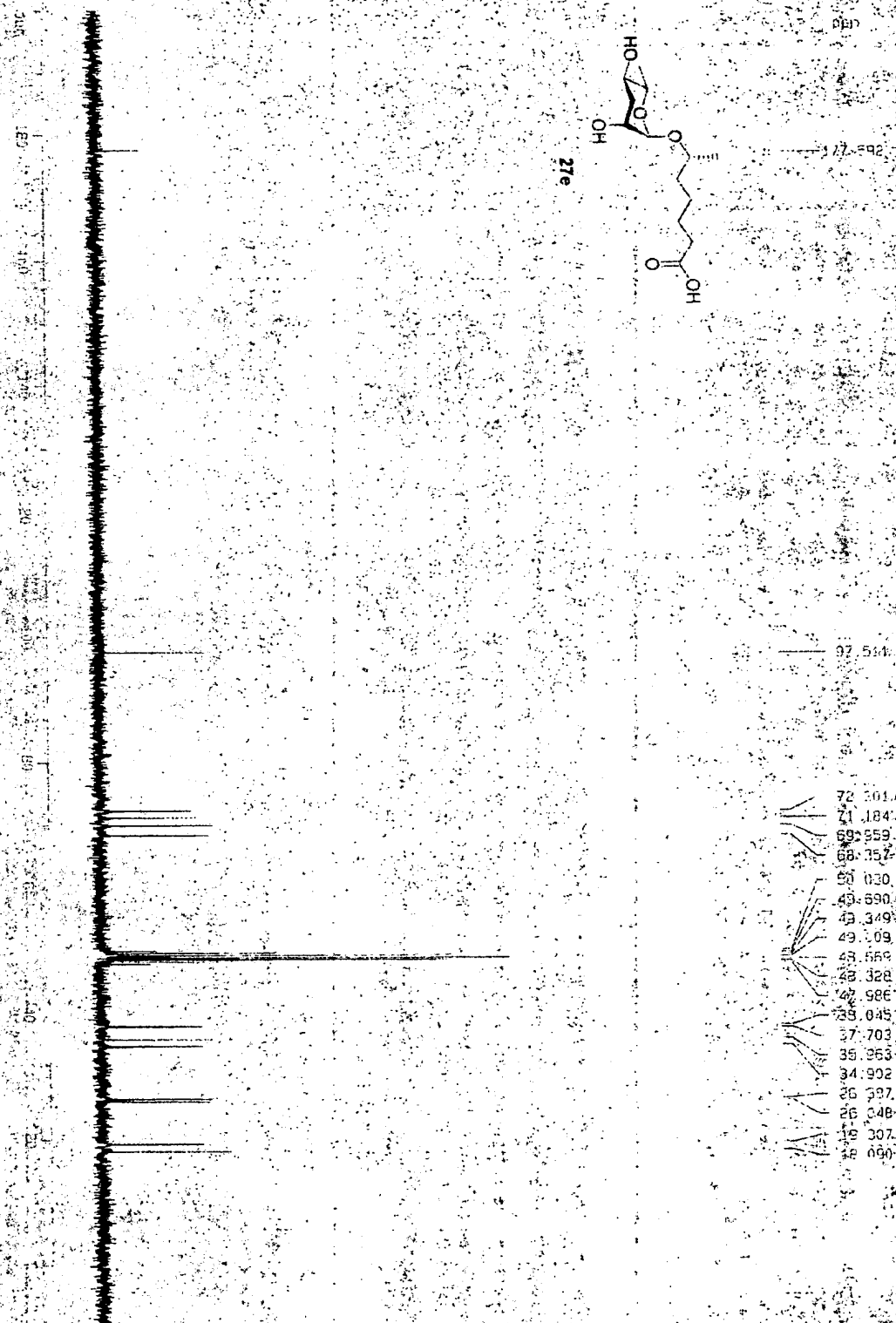
[Fig. 2]



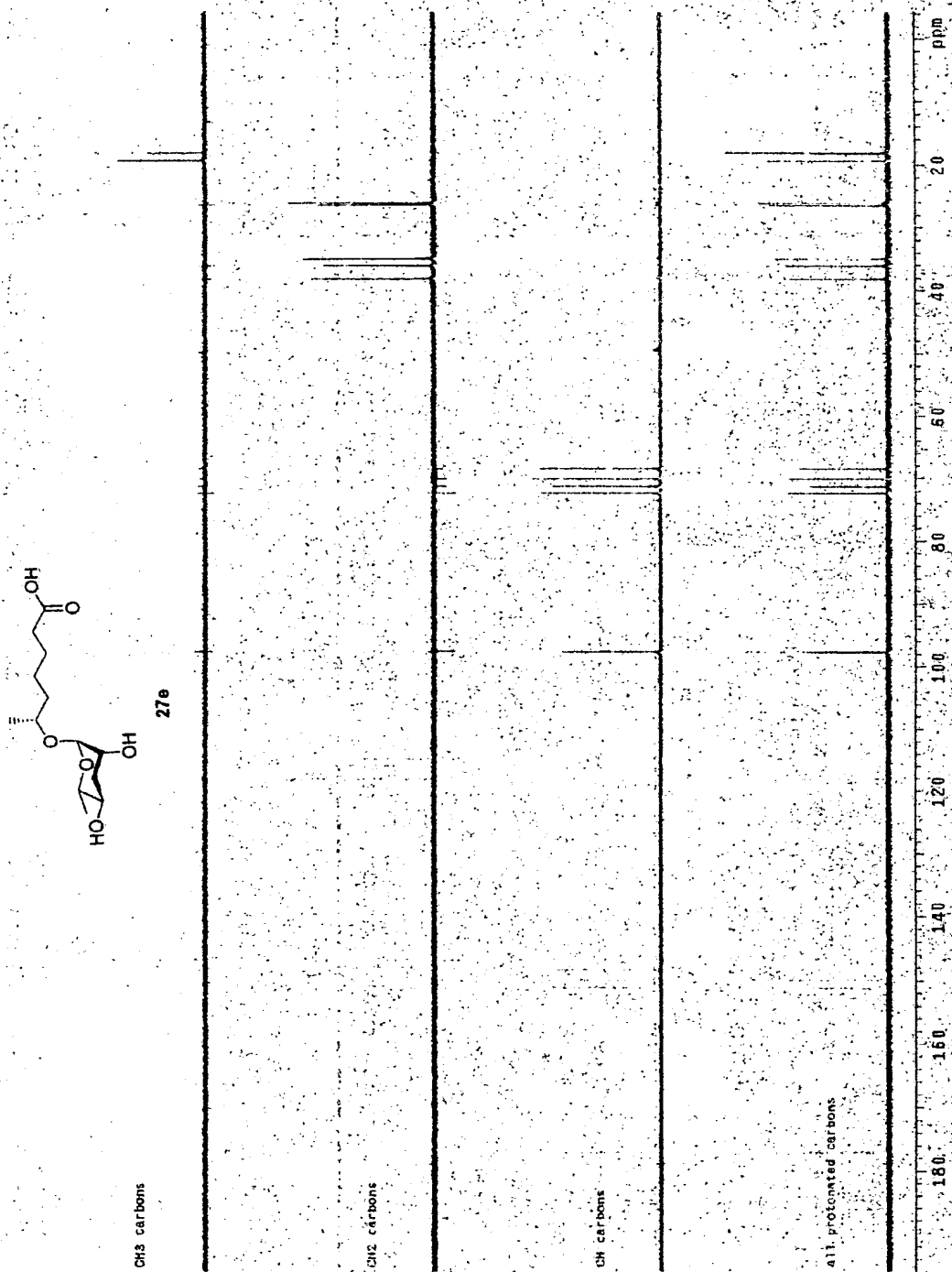
[Fig. 3]



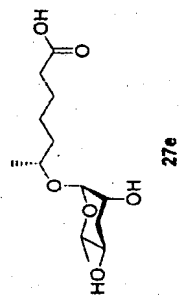
[Fig. 4]



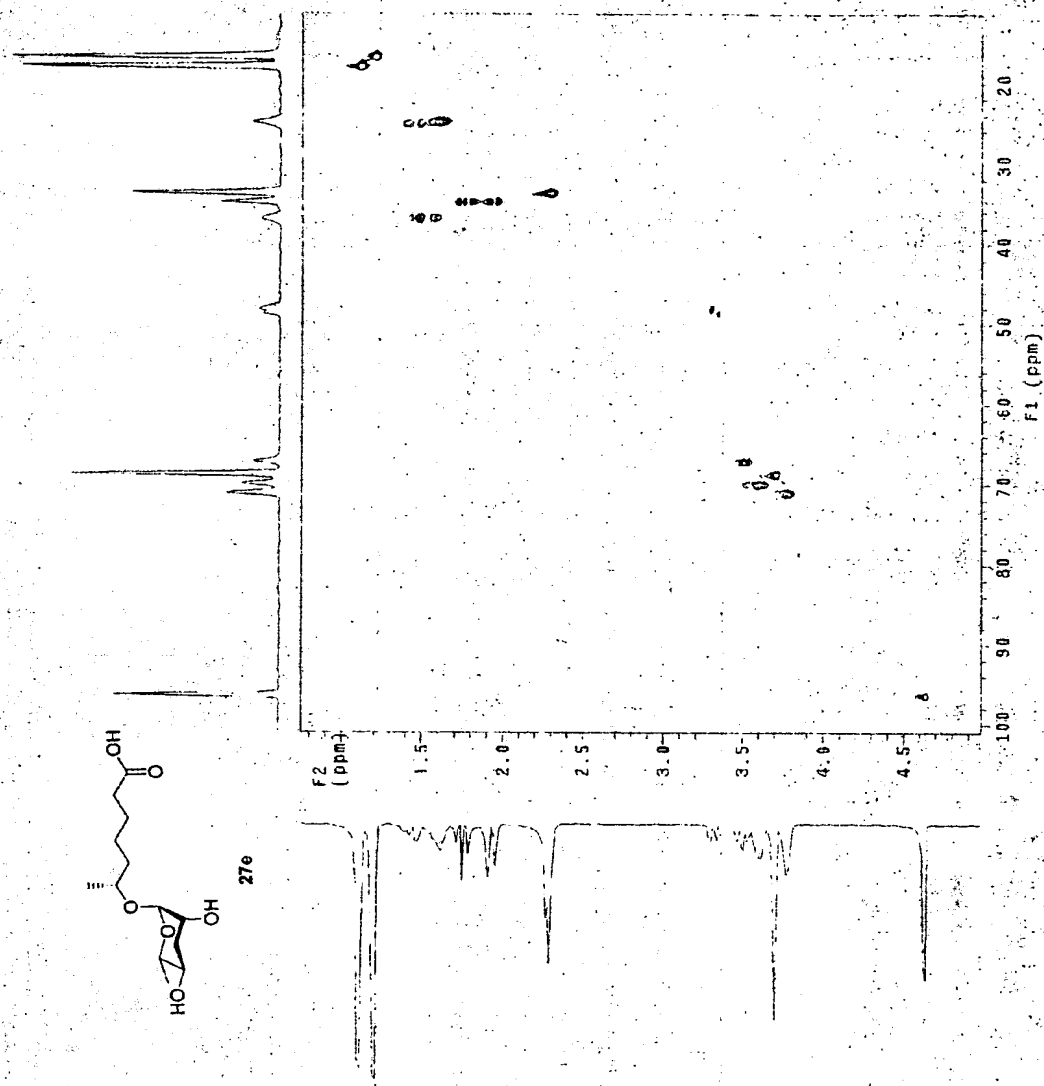
[Fig. 5]



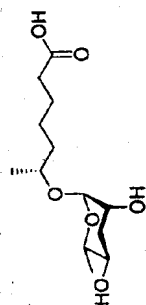
**27e**



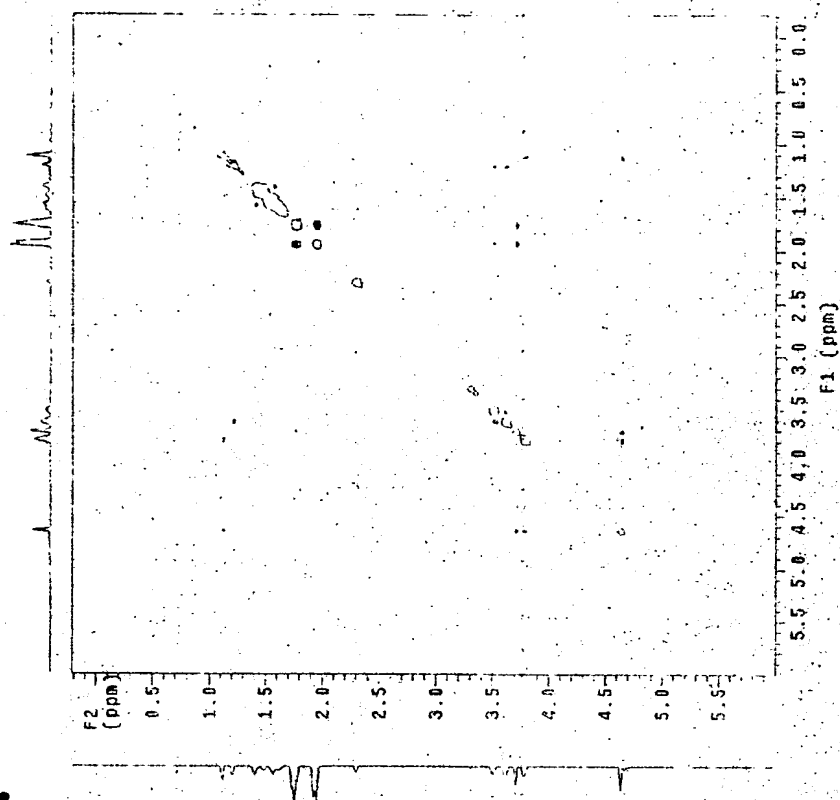
[Fig. 7]



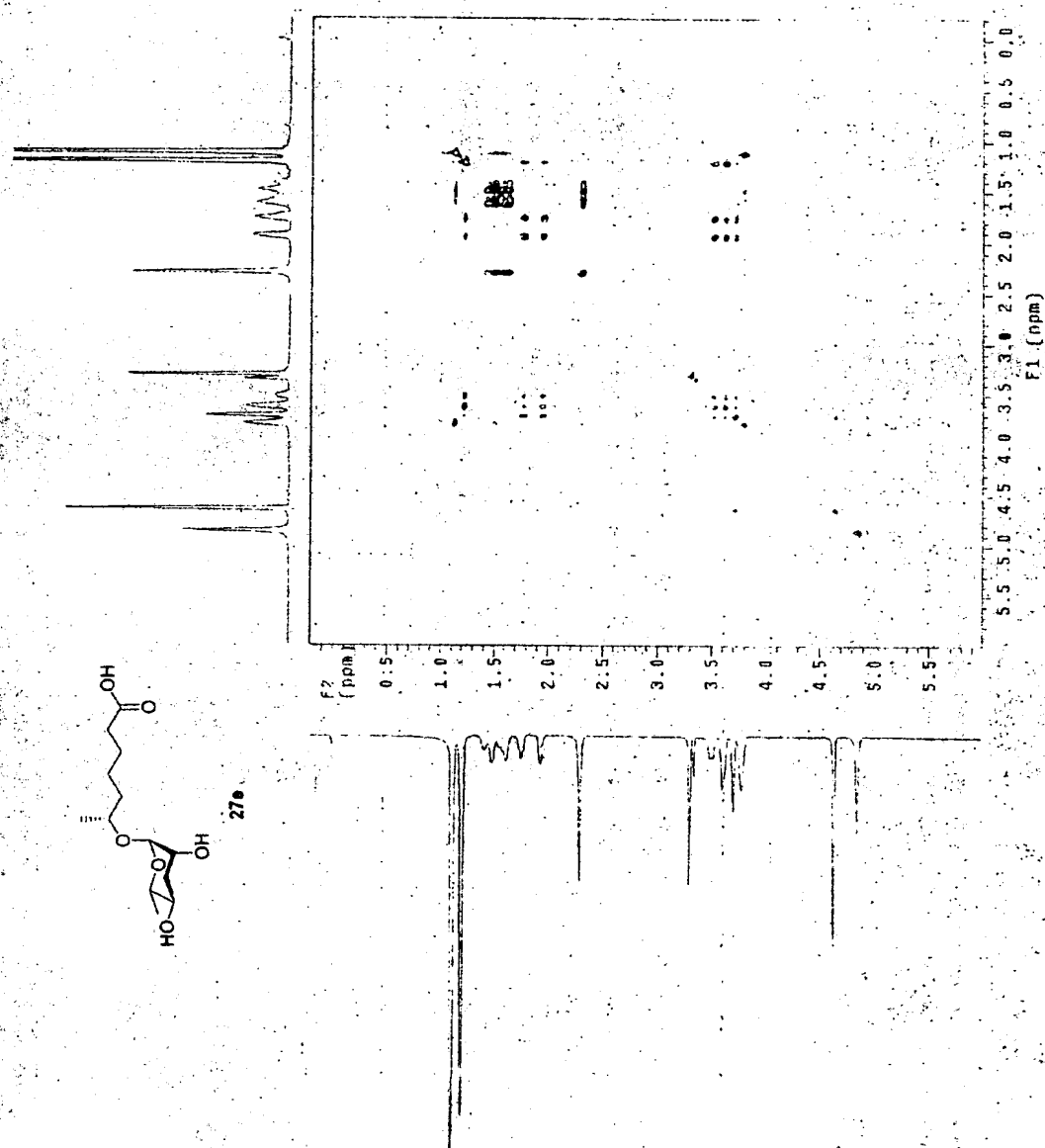
[Fig. 8]



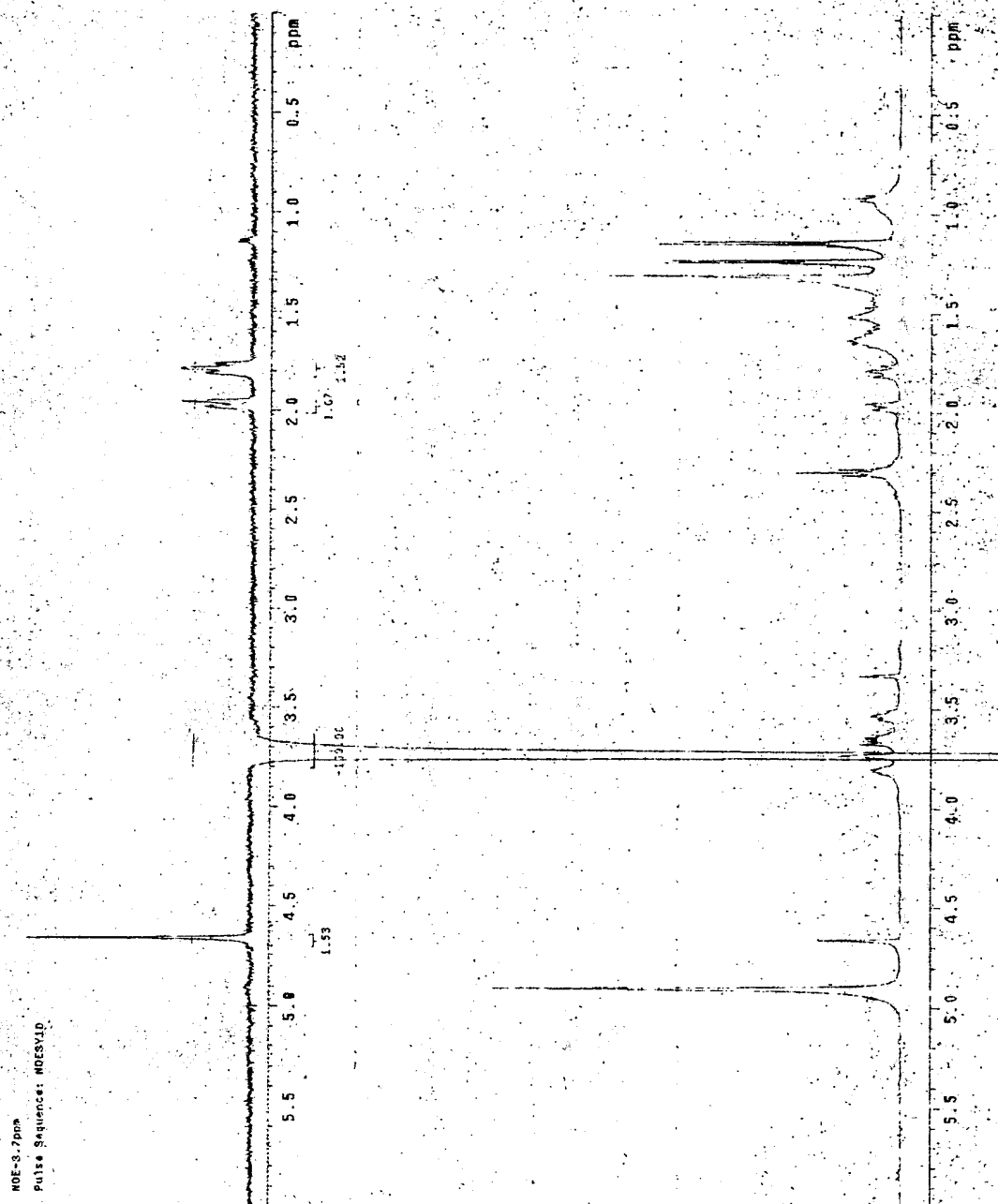
27



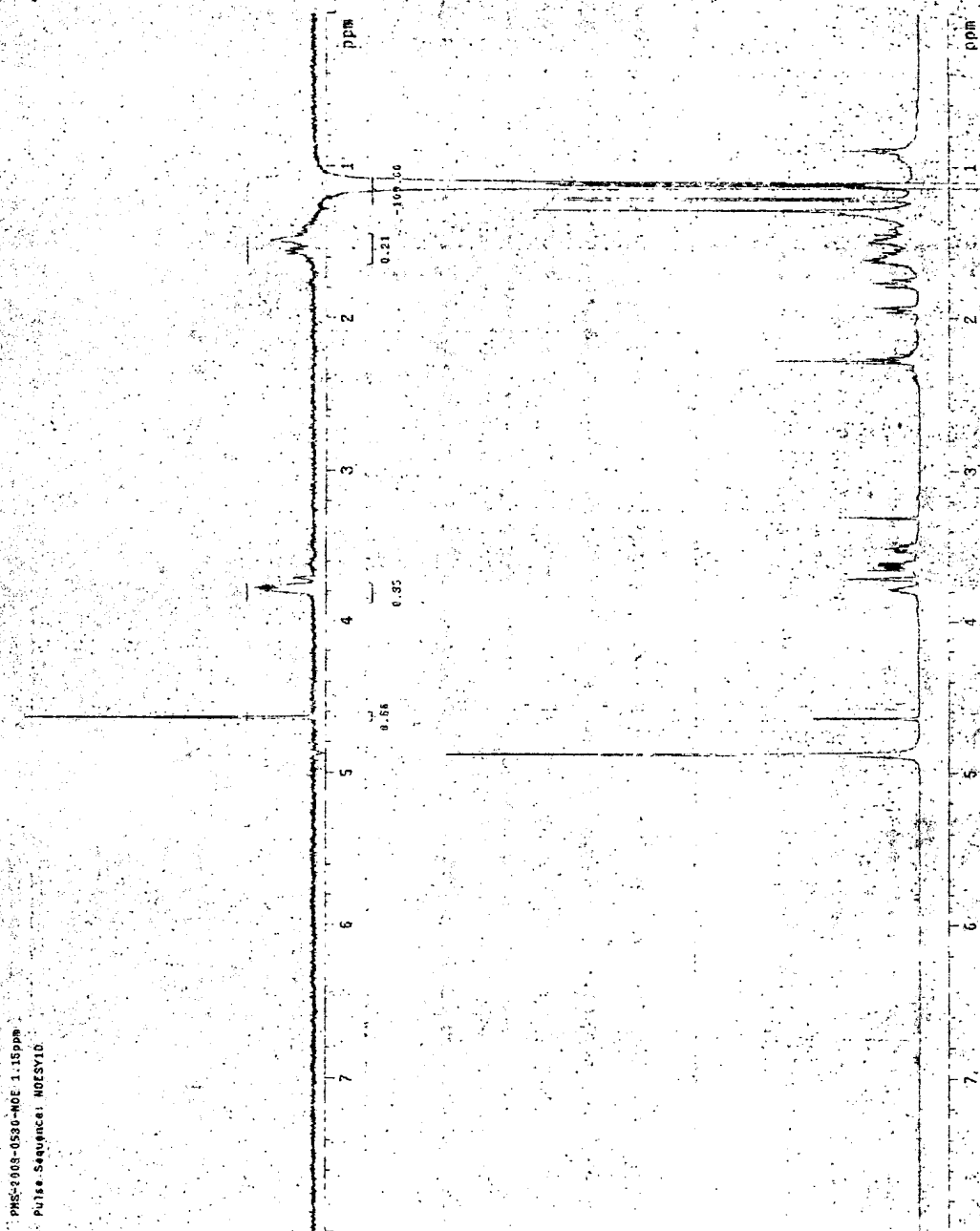
[Fig. 9]



[Fig. 10]

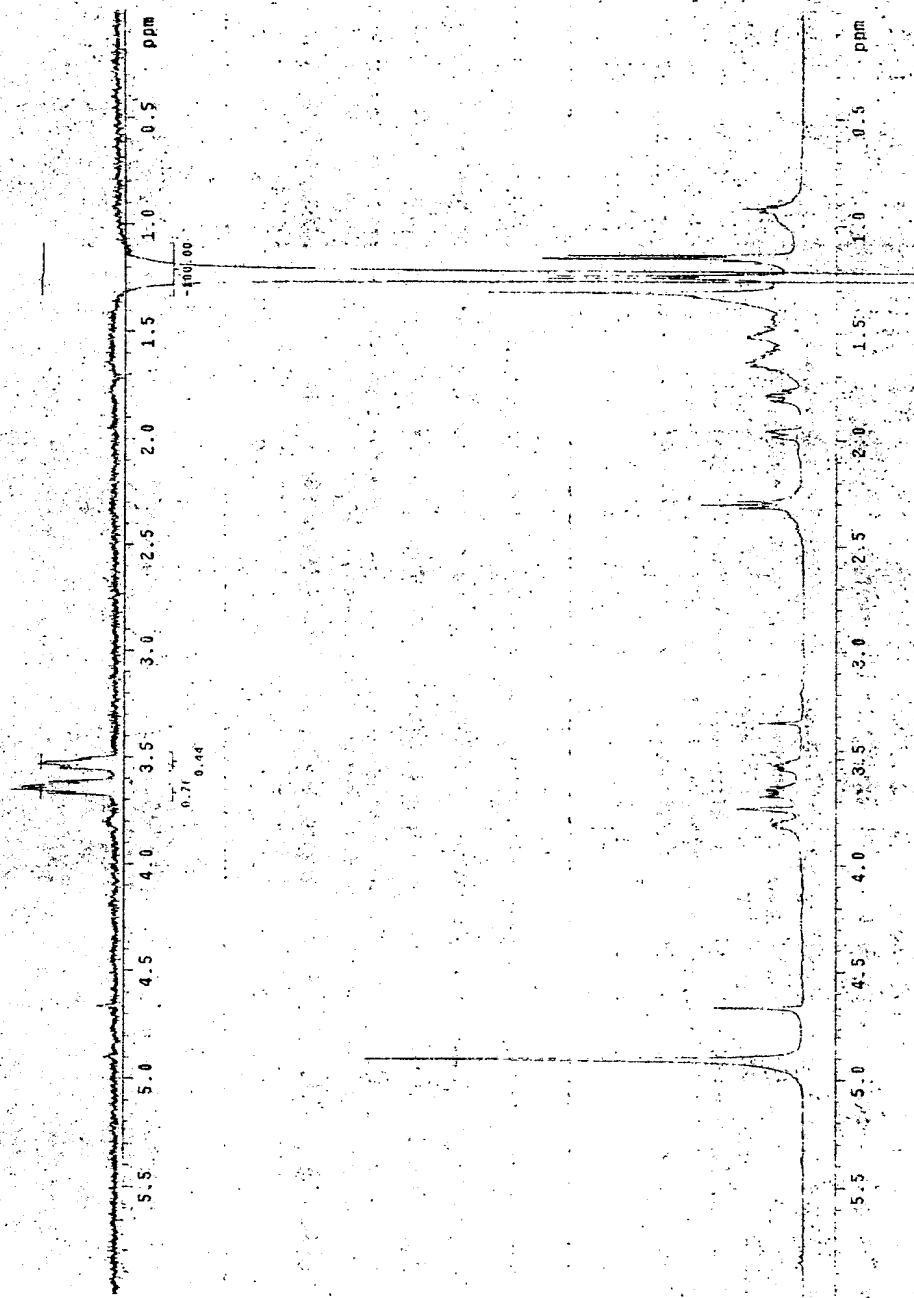


[Fig. 11]



[Fig. 12]

MDI-3.2Pip  
Pulse Sequence: NOESY1D



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/KR2004/002948**A. CLASSIFICATION OF SUBJECT MATTER****IPC7 C07H 15/04**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

\*IPC 7 C07H, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Korean Patent and Application for Inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ON LINE, USPTO, Chemical Abstract

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Yoshikawa, K. et al. "Four acylated triterpenoid saponins from Albizia procera" J. Natural Products 1998 Vol.61(4) pages 440-445 See the entire document	1 - 14
A	Russa R. et al. "Partial structure of lipopolysaccharides isolated from Rhizobium leguminosarum bv. trifolii 24 and its GalA-negative exo-mutant AR20" Systematic and Applied Microbiology 1996 Vol.19(1) pages 1-8 See the entire document	1 - 14
A	van Swinderen B. et al. "A-C. elegans pheromone antagonizes volatile anesthetic action through a go-coupled pathway" Genetics 2002 May Vol.161(1) pages 109-119	1 - 14
P, X	KR 1020040042338-A (Paik, Young Ki et al.) 20 May 2004 See the entire document	1 - 14

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Date of the actual completion of the international search

03 MARCH 2005 (03.03.2005)

Date of mailing of the international search report

04 MARCH 2005 (04.03.2005)

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

PCT/KR2004/002948

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
KR 1020040042338 A	20 May 2004	None	None

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